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Analysis of CB_1 and CB_2 receptor levels in the *post-mortem* spinal cord and motor cortex of amyotrophic lateral sclerosis patients

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Introduction: Motor neuron disease (MND) includes several neurological disorders that selectively affect motor neurons, with amyotrophic lateral sclerosis (ALS) being the most common disorder in this group. ALS is a degenerative disease produced by the damage of the upper and lower motor neurons leading to muscle denervation, atrophy and paralysis. Recent data support that the endocannabinoid system plays an important role in the pathogenesis of ALS, a fact derived from studies conducted in several animal models of ALS. Our objective has been to perform a complete characterization of the endocannabinoid system in the spinal cord and motor cortex of MND (including ALS) patients.

Methods: *Post-mortem* tissues received from Brain Bank tissue Biobank, Kings College, London, and obtained from well-characterized patients diagnosed of MND and age- and gender-matched control subjects, were used for analysis of different endocannabinoid receptors and enzymes, using immunostaining and western blotting.

Results: We have found a decrease in the number of Nissl-stained motor neurons in the spinal ventral horn in MND patients compared with controls. Elevations in glial markers (Iba-1 and GFAP) were also evident in MND patients in both the spinal cord and the motor cortex. As regards to endocannabinoid elements, the western blotting analysis of CB2 receptors levels were increased in the motor cortex, but this parameter remained unaltered in the spinal cord of MND patients. By contrast, CB1 receptor levels were significantly reduced in the spinal cord in agreement with the already shown loss of spinal motor neurons, whereas they were not altered in the motor cortex. No changes were found in endocannabinoid degrading enzymes FAAH and MAGL, using immunostaining, in both CNS structures.

Conclusion: We have confirmed that certain elements of the endocannabinoid signaling, in particular the CB1 and CB2 receptors, are altered in ALS patients compared to control subjects, depending on the specific CNS area. Such changes support the idea that targeting these elements may serve for the development of a neuroprotective therapy in ALS.